Crystal Solubility: Importance, Measurement and More

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Industry Demand Led Research

*Accelerate the adoption of continuous processing in pharmaceutical manufacturing*

- Improve particulate based product supply via continuous processes
- Develop understanding of complex interactions between process, materials and quality
- Implement flexible continuous process technologies that deliver benefits:
  - Robustness
  - Consistency
  - Manufacturability
  - Performance
**Product**
- Complex multicomponent systems

**Process**
- Flexible and sustainable production facilities

**Phenomena**
- New level of understanding for prediction and control

**Crystal Nucleation**

**Chiral resolution**

**Pharmaceutical & Protein Crystallisation**
Crystal Solubility
Binary Systems

Intermolecular interactions between solute and benzene are essentially *identical*.

Phenanthrene

Anthracene

Benzene
Crystal Solubility

Binary Systems

**Phenanthrene**

\[ x^* = 20.7 \text{ mol}\% \]

\[ T_m = 100°C \]

Intermolecular interactions in **Anthracene** crystal are much larger than in **Phenanthrene** crystal:

**Anthracene** prefers the solid phase

\[ x^* = 0.81 \text{ mol}\% \]

\[ T_m = 217°C \]
Crystal Solubility

Binary Systems

Solubility is determined by intermolecular interactions in both solution and solid.

Phenanthrene in Benzene

Anthracene
Crystal solubility $C^*$:
The solution concentration that is in equilibrium with the crystalline solid at a specific temperature $T$ and pressure $P$. 

100% pure Crystalline phase

Solution with Concentration $C^*$
At temperature $T$, Pressure $P$
Crystal Solubility

• Crystallization
• Solubility Measurements
• Solubility Analysis
• Solubility Measurements in Complex Multicomponent Systems
• Solubility in Complex Multicomponent Systems
• Crystallization Kinetics
Crystallization from Solution

Synthesis of API → Single stage Crystallization → Filtration

Crystalline product 99.99% pure
Solution containing impurities and dissolved synthesis product
Crystallization from Solution

- Solution
  - Primary nucleation
    - supersaturation
      - agglomeration
        - Secondary nucleation
          - crystal growth
            - hydrodynamics
          - crystal size distribution
            - crystal shape
              - purity
              - solid form
    - Product quality
      - Productivity
Crystallization from Solution

![Graphs showing concentration vs. temperature and solubility vs. w% of antisolvent.](attachment:\data\graphs.png)

- **Supersaturated**
- **Undersaturated**

**Equation:**

\[
S = \frac{a_A \cdot a_B}{K}
\]

Where:
- \(S\) is the solubility
- \(a_A\) and \(a_B\) are the activity coefficients
- \(K\) is the equilibrium constant
Crystallization from Solution
Binary Systems

**Concentration**

**Temperature**

**Solubility**

- **Supersaturated**
- **Undersaturated**

**Heat**
Crystallization from Solution
Binary System at constant P,T

Concentration $C = 100 \text{ mg/ml solvent}$
Solubility $C^* = 20 \text{ mg/ml solvent}$

$Yield \ C - C^* = 80 \text{ mg crystals/ml solvent}$

80% is crystallized, 20% remains in solution

The solubility curve is the first step towards a crystallization process design
Crystal Solubility

- Crystallization
- Solubility Measurements
- Solubility Analysis
- Solubility Measurements in Complex Multicomponent Systems
- Solubility in Complex Multicomponent Systems
- Crystallization Kinetics
Crystal solubility $C^*$:
The solution concentration that is in equilibrium with the crystalline solid at a specific temperature $T$ and pressure $P$. 

[Image: 100% pure Crystalline phase. Solution with Concentration $C^*$ At temperature $T$, Pressure $T$.]
**Equilibrium Method**

- Equilibrate suspension at constant temperature, pressure
- Sample solution & analyze concentration
  - HPLC
  - Gravimetric
  - Etc.
- **Accurate**
- **Time consuming**

Temperature [°C] vs Concentration [mg/mL]
Temperature Variation Method

Clear point temperature

Suspension (Low T)  Clear solution (high T)

Clear point temperature:
The temperature at which a suspension becomes a clear solution during heating with a certain rate
Temperature Variation Method

Clear point temperature

- Increase solubility until suspension turns into a clear solution
- Reproducing results fairly quick
- Also metastable zone width

Temperature [°C]

Change solubility

Concentration [mg/mL]
Clear & Cloud Point Measurements

Clear point, 100% transmission

Ts = 42.2°C

Ts = 42.3°C

Heating rate = 0.3°C/min

1440 min = 1 day
Clear Point & Solubility

Concentration = Constant

If:
- Crystal detection limit is low
- Dissolution is fast
- No fouling
- No crowning
- ...

Look at the vials!

Often, a heating rate of 0.3°C/min gives sufficiently accurate data.
Crystal Solubility

- Crystallization
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- Solubility Analysis
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Solubility Diagram
Of isonicotinamide (INA) in Ethanol

![Graph showing solubility of isonicotinamide in ethanol versus temperature. The x-axis represents temperature in °C, ranging from 0 to 75. The y-axis represents concentration in mmol/mol, ranging from 0 to 80. The graph shows a positive trend indicating increased solubility with increasing temperature.]
**Solubility**

**Solubility ideal system:**

Enthalpy of fusion of pure A

\[ x^* = \exp\left(-\frac{\Delta H}{R} \left( \frac{1}{T} - \frac{1}{T_m} \right) \right) = \exp\left(\frac{A}{T} + B\right) \]

Fitting the solubility data of a real system:

\[ \ln x^* = \frac{A}{T} + B \]
Van ’t Hoff-plot
Of isonicotinamide (INA) in Ethanol

Fitting equation:
\[ \ln x^* = \frac{A}{T} + B \]

Convenient and accurate to extrapolate
Van ‘t Hoff-plot
Of isonicotinamide (INA) in Ethanol

Fitting equation:
\[ \ln x^* = \frac{A}{T} + B \]

Ideal solubility:
\[ \ln x^* = -\frac{\Delta H}{R} \left( \frac{1}{T} - \frac{1}{T_m} \right) \]

Why is there a difference between ideal and real solubility?
Chemical Potential

Ideal system

\[ \mu_{eq}^L = \mu_{eq}^* + kT \ln x_{eq} \]

Real system

\[ \mu_{eq}^L = \mu_{eq}^* + kT \ln a_{eq} \]

The activity coefficient \( \gamma \) describes non-ideality

\[ a = \gamma x \]
Crystal Solubility

- Crystallization
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- Crystallization Kinetics
Co-crystallization

Of isonicotinamide (INA) and Carbamazepine (CBZ) in Ethanol
Pure Component Solubility

Of isonicotinamide (INA) and Carbamazepine (CBZ) in Ethanol

T = 25°C

**INA**
\[ x^* = 33.3 \text{ mmol/mol} \]
\[ c^* = 72 \text{ mg/ml} \]

**CBZ**
\[ x^* = 5.7 \text{ mmol/mol} \]
\[ c^* = 24 \text{ mg/ml} \]

Solubility of **INA** is 6 times higher than that of **CBZ**
Solvent Addition Method

Clear point concentration

- Change the composition until clear point concentration at constant temperature

- Faster than Equilibrium Method
- Suitable for multicomponent systems
- No limitation # components in sample and added solution
Solvent Addition Method

2x4 Syringe Pumps: Each syringe can hold a different solvent composition. Two different flow rates can be tested in one go.

Crystalline: 8 Reactors with independent temperature control and PVM
Co-crystal Phase diagram

Carbamazepine (CBZ)
Isonicotinamide (INA)
Ethanol

T = 20°C

Legend:
- solubility CBZ
- Solubility INA
- Solubility Cocrystal
Crystal Solubility

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- Solubility Measurements
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- Crystallization Kinetics
Polymorphism: The ability of a chemical compound to form 2 or more crystal structures
The clear point temperature depends on the polymorph that is present in the suspension.
Complex Phase Behavior

Salt, Co-crystal, solvate:
The crystal phase might contain more components in specific ratios

Solid Solution:
The crystal phase might contain more components in varying ratios

M. Matsuoka, 1978
Chirality

Introduction
Chiral compounds

Binary phase diagram

Conglomerate
Racemic compound
Solid solution

The phase diagram reflects the kind of solid state
Chiral Compound Solubility
Asparagine in Water

Ternary phase diagram screening

Sample composition

\[ y_R = \frac{x_R}{x_R + x_S} \]

Clear point temperatures

Conglomerate
Chiral Compound Solubility: Ibuprofen in Hexane

Ternary phase diagram screening

\[ y_R = \frac{x_R}{x_R + x_S} \]
Chiral Compound solubility:
Atenolol in Ethanol

Ternary phase diagram screening

S. Sukanya, J.H. ter Horst,
Racemic Compound, Conglomerate, or Solid Solution: Phase Diagram Screening of Chiral Compounds,
Crystal Solubility

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Metastable Zone Width

Temperature [°C]

Transmission of light [%]

Time (hour)
Measuring Induction Times

The time until detection of crystals at a constant supersaturation

- Accurate temperature control

![Graph showing temperature and transmission over time with a 1 ml sample](image)
Measuring Induction Times

- Create constant supersaturation
- Measure induction time
- Do this a large number of times, say $M$ times

\[ P(t) = \frac{M^+ (t_i)}{M} \]
### Induction Time Distributions

<table>
<thead>
<tr>
<th>$S$ [-]</th>
<th>$J$ [m$^3$s$^{-1}$]</th>
<th>$t_g$ [min]</th>
<th>$J$ [m$^3$s$^{-1}$]</th>
<th>$t_g$ [min]</th>
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<td>275</td>
<td>4.7</td>
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<td>-1</td>
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</tbody>
</table>

Crystal Solubility

- Crystallization
- Solubility Measurements
- Solubility Analysis
- Solubility Measurements in Complex Multicomponent Systems
- Solubility in Complex Multicomponent Systems
- Crystallization Kinetics
Crystal Solubility

- All crystalline compounds behave differently
- The temperature dependent solubility of a compound in a solvent is the first step towards a crystallization process design
- Temperature measurement methods
  - Gravimetric, temperature variation, solvent addition
- Metastable zone width, induction times and crystal nucleation rates
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